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# Excited delirium syndrome (ExDS): Redefining an old diagnosis

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ABSTRACT

Recently, the National Institute of Justice (NIJ) of the United States of America convened a meeting of experts in the area of Excited Delirium Syndrome (ExDS). The history of ExDS, the clinical presentation, the pathophysiology, differential diagnoses and management options were discussed. Though the specific pathophysiological pathways of ExDS have yet to be formally defined, considerable research has been undertaken on this topic. It is important for law enforcement, medical and other healthcare professionals to be familiar with current knowledge about the syndrome. This paper summarizes the current state and knowledge of ExDS.



## 1. Introduction

The formation of the ExDS Workshop Panel and the examination of this issue was a requirement derived from the NIJ's Technology Working Group (TWG) on Less-Lethal Devices. The Panel included members from the field of law enforcement, including active field officers and trainers, emergency physicians, psychiatrists, forensic physicians, forensic pathologists, molecular biologists and scientists (see Table 1). The group met in April, 2011 to review available data and provide feedback on directions the NIJ should consider in the future, with the specific goal of reducing deaths in subjects with symptoms consistent with ExDS.

Traditionally, the forensic medical community has classified patients who presented with altered sensorium and aggressive agitated behavior, and a combination of other symptoms including "superhuman" strength, diaphoresis, hyperthermia, propensity to break glass, attraction to light or lack of willingness to yield to overwhelming force, who then died with a positive drug screen for sympathomimetic agent, and no other anatomic cause of death, as an "Excited Delirium" death. In recent years, it has become increasingly clear that many patients with this constellation of symptom's and signs have been managed in emergency departments for decades and in only a small minority of cases is the outcome fatal. The clinical phenomenon was described in the 1800s, but only in recent years has a clearer understanding developed about this syndrome and a recognition that research needs to be directed to identifying the underlying pathophysiological and cellular mechanisms.

## 2. Is Excited Delirium always fatal?

The term "Excited Delirium" has been used to refer to a subcategory of delirium that has primarily been described retrospectively in the forensic literature. For that reason, many have felt the diagnosis required sudden death of the individual. Law enforcement and emergency medical services (EMS) in the USA have many years of experience of dealing with ExDS patients. Individuals with ExDS most frequently come to the attention of law enforcement professionals because of the associated violent, agitated, and erratic behavior. Emergency medical services are often called to sedate or transport over-stimulated ExDS subjects after the individual has been arrested and restrained, or to treat victims of ExDS-associated cardiac arrest. These out-of-hospital ExDS subjects have traditionally been transported to custody and survived, transported to the hospital and survived, or have a sudden cardiac arrest with death ensuing. If death occurs, a forensic autopsy is required. When the outcome is fatal, medical examiners will, in the absence of other apparent causes of death, typically rule that death is a consequence of excited delirium. Thus, this presentation bias had led to the development of the concept that ExDS is always a fatal condition.

The concept of excited delirium has become a matter of increasing concern for emergency physicians and other primary care health professionals as many work with policing agencies responsible for the policy and procedures and are used in the field

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**Table 1**
Members of the National Institute of Justice Technology Working Group (TWG) on Less-Lethal Devices who met in Seattle, WA on April 2011 (this manuscript does not reflect this group's opinions. They are listed as credit to their participation in the TWG).

| |
|---|
| Dr. Cindy Bir (Wayne State University) |
| Dr. W. Bosseau Murray (Penn State) |
| Dr. Bill Bozeman (Wake Forest University) |
| Amanda Brooks |
| Officer Tom Burns (Seattle Police Department) |
| Dr. David Carlbom (University of Washington) |
| Mr. Joe Cecconi (NIJ/DOJ) |
| Dr. Michael T. Compton (G. Washington University) |
| Dr. Marcus Copus (University of Washington) |
| Dr. Donald Dawes (Lompoc Valley Medical Center) |
| Dr. Andrew Dennis (Cook County Sheriff) |
| Ms. Theresa G. Di Maio |
| Dr. Vincent J.M. Di Maio |
| Sgt Fred Farris (Lenexa Police Department) |
| Dr. Chris Hall (Vancouver Island Health Authority) |
| Dr. Richard Harruff (Chief Medical Examiner, King County) |
| LTC (USA-Ret) Ed Hughes (Penn State) |
| Sgt Joel Johnston (Vancouver Police Department) |
| Dr. Steven Karch (University of Miami) |
| Dr. William Kraemer (University of Connecticut) |
| Tom Linn |
| Col (USMC-Ret) Andy Mazzara (Penn State) |
| Sgt Brian Muller (Los Angeles County Sheriff's Department) |
| Keith Murray (Chicago) |
| Officer Chris Myers (Seattle Police Department) |
| Norm Nedell (Seattle Medic One) |
| Dr. Jason Payne-James (UK-Consultant Forensic Physician) |
| Dr. Darrell L. Ross (Valdosta State University) |
| Dr. Kent E. Vrana (Penn State-Pharmacology) |
| Dr. Gary M. Vilke (University of California San Diego) |
| Dr. Mary Williams (JNLWD – ASC) |
| Mr. Rick Wyant (Washington State Patrol) |

to advise on and manage these patients. Earlier recognition, intervention and proactive treatment might result in fewer deaths from this syndrome.

## 3. Case definition

Clinical identification, and therefore identification of ExDS is challenging; the spectrum of behaviors and clinical signs overlap with many other disease presentations. Evaluation and subsequent treatment interventions directed at these alternate diagnoses, such as hypoglycemia or hyperthyroidism, may potentially resolve the clinical symptoms and findings of the subject who has symptoms consistent with ExDS. Faced with the lack of a clear definition and pathophysiologic etiology, ExDS has more recently been defined as a *syndrome* instead of a unique disease.

The American College of Emergency Physicians (ACEP) recently supported a Task Force that was charged with reviewing the current state of the medical literature on the topic of ExDS. The group was also tasked with finding ways to educate emergency physicians about the problem. These recommendations were published on the ACEP website as a formal White Paper accepted by the ACEP Board of Directors. Though many of the deaths from ExDS may not be preventable, there is likely to be a subset of patients where early treatment might be life saving. At the current time, based on the best medical evidence, it is impossible to know how many patients have been saved by emergent therapy. The National Association of Medical Examiners (NAME) had accepted the term "Excited Delirium" a number of years ago.

## 4. History of ExDS

In the 1800s, Dr. Luther Bell, the primary psychiatrist at the McLean Asylum for the Insane in Massachusetts was the first to describe a clinical condition with a 75 percent mortality rate. The behavior described in these cases, or cases with a similar constellation of symptoms and features, has been referred to "Bell's Mania." For more than 150 years there have been dozens of case reports of the same symptom complex, but with different names. These have included, but are not limited to, "manic-depressive exhaustion", "lethal catatonia", "acute delirious mania", "acute psychotic furors exhaustive syndrome", and "typhoma". These patients all manifested clinical findings and outcomes that are extremely similar to of the symptoms of what we refer to today as ExDS.[1] These historical cases primarily occurred at facilities and institutions that housed mentally disturbed individuals.

Reports of ExDs-like cases appear to be absent from medical journals by the mid-1950s.[2] This decline in deaths has been largely attributed to the initiation of antipsychotic pharmaceutical therapy. Medications, like thorazine, changed psychiatric practice from one of monitoring and observing, to one of active intervention with the aid of pharmacologic treatment. Very often, the result was subsequent de-institutionalization and community placement.

Then, in the 1980s, a number of case reports and case series were published, each describing patients with similar behavior noted by Bell and others 100 years earlier. However, in these "modern" cases, very few were related to undiagnosed or untreated psychiatric illness but, rather, appeared to be associated with cocaine abuse and their appearance coincide with the introduction of cocaine into the United States.[3,4] In addition, other drugs, including methamphetamine, phencyclidine (PCP) and lysergic acid diethylamide (LSD) which have also been linked to the occurrence of this syndrome.[5–10]

In 1985 a subset of cocaine deaths was described in a paper by Wetli and Fishbain. In that paper the term "excited delirium" was coined.[11] The group of patients they were describing had acute cocaine intoxication, but not an overdose, and often there was a history of mental illness, particularly conditions involving paranoia. Because these patients always presented with agitated behavior, law enforcement was often called to the scene. The usual outcome was a struggle, often involving the use of other physical or chemical control measures, including use of conducted energy weapons (CEW), OC spray and, ultimately restraint. Typically, after police had restrained the patient, sudden and unexpected death occurred. Autopsies, which did not include histochemical or neurochemical examination, did not reveal a definite cause of death, although trauma and natural disease were excluded.

## 5. Is ExDS a diagnosis?

The argument about whether ExDS is an actual diagnosis mainly centers on the issue that certain organized medical associations, particularly the American Medical Association (AMA) and the American Psychiatric Association (APA) do not recognize ExDS as a diagnosis.[12] Their failure to do so hinges on the fact that the medical coding reference materials, including the International Classification of Disease, Ninth Revision (ICD-9), do not recognize the exact term "excited delirium" or "excited delirium syndrome."[13] However, the National Association of Medical Examiners (NAME) and the American College of Emergency Physicians (ACEP), the most likely physicians to encounter these patients, do recognize ExDS as a discrete diagnostic entity.

The ICD-9 does have billing codes that describe the clinical presentation of ExDS patients, including 96.00S Manic Excitement, 293.1J Delirium of Mixed Origin, 292.81Q Delirium, drug induced, 292.81R Delirium, induced by drug, 307.9AD Agitation, 780.09E Delirium, 799.2AM Psychomotor Excitement, 799.2V Psychomotor Agitation, and 799.2X Abnormal Excitement. As a unifying diagnostic term was not required to charge for providing care to these patients in the emergency department, there was no financial

incentive to unify all of these conditions under one diagnosis. Psychiatrists only occasionally encounter patients presenting with ExDS; most often these patients are treated in custodial facilities and emergency departments, because their symptoms are usually thought to be a consequence of drug abuse.[14]

## 6. Epidemiology

As there is no current standardized case definition with which to identify ExDS, the exact frequency of ExDS is unknown. Almost nothing has ever been published about survivors. This had led many to spurious perception that ExDS is uniformly fatal.

Emergency physicians who were members of the ACEP ExDS Task Force reported caring for multiple patients with ExDS who had, indeed survived, and at least one published observational study suggests that the incidence of death among patients manifesting signs and symptoms consistent with ExDS is less than 10%.[9] An exact figure is difficult to determine because it is believed that repetitive exposure to triggering substances, such as methamphetamine, cocaine or mental health medications, can lead to a kindling event in the brain that starts the patient down the progressive path of ExDS, with each subsequent presentation becoming progressively worse until death occurs.[15,16] A review of the literature also reveals common characteristics among patients identified post-mortem as suffering from ExDS. More than 95% of all published fatal cases involve men and their mean age is 36 years.[17–24] These subjects present as extremely agitated or aggressive with bizarre behavior, and are quite often impervious to pain, combative, hyperthermic or hot to the touch, sweaty and tachycardic. Additionally, many are naked or under-clothed for their environment, drawn to water, lights or glass products. The majority of cases involve stimulant abuse, most commonly cocaine, though methamphetamine, PCP, and LSD have also been described.[25,26]

The other cohort of ExDS cases and deaths are reported to be patients with psychiatric illnesses who abruptly stop taking their psychotherapeutic medications.[27] This has raised the question of whether the presenting symptoms and finding seen in this population represent withdrawal syndromes from the medications involved, central nervous system adaptations to medications, or escalation of underlying untreated disease. Less commonly, persons with new-onset psychiatric disease, particularly with manic or psychotic features, can present with ExDS.[14] In most cases, the underlying disease will be untreated at the time of presentation, but in some instances the disease may be partially treated or mistreated.

In many, if not most reported cases, cardiac enlargement has been found at autopsy.[28,29] For example, in the 18 cases described by Stratton,[9] the mean heart weight was 419 g versus the (height adjusted) weight predicted by standard normograms of 321 grams.[30] This may just be an epiphenomenon explained by the fact that most reported cases have involved chronic cocaine and methamphetamine abusers. Chronic use of either drug results in myocardial hypertrophy.[16]

In a study by Hall et al, the presence or absence of ten potential clinical features of ExDS were recorded by Canadian police for cases seen in over 1 million police–public interactions over a two-year study period.[31] The features of ExDS studied included pain tolerance, tachypnea, sweating, agitation, tactile hyperthermia, police non-compliance, lack of tiring, unusual strength, inappropriately clothed, and mirror or glass attraction. Of the 698 encounters involving use of force, probable ExDS cases were identified in 3.4% ($n = 24$). These probable cases were defined based upon the presence of perceived abnormal behavior including agitation and at least 6 of the 10 potential clinical criteria for ExDS. When looking at the population who manifested 7 or more features including tactile hyperthermia, 18 (2.7%) of the use of force cohort met criteria for ExDS.

## 7. Pathophysiology

The actual pathophysiology of ExDS is complex and not well understood. Currently there are no clear reasons why some patients progress to death and why some do not, but a kindling effect may offer a possible explanation.

Stimulant drug use, especially cocaine, is associated with ExDS.[17,19,20,21,24,32] Of note, post-mortem toxicological analysis of fatal cocaine-associated ExDS patients demonstrates cocaine concentrations similar to those found in recreational drug users and less than those noted in acute cocaine intoxication deaths, suggesting a different mechanism of death.

Anatomic and molecular evaluation of ExDS patients who die has focused primarily on post-mortem brain examinations. Results from this increasingly robust body of work demonstrate a characteristic loss of the dopamine transporter in the striatum of chronic cocaine abusers who die with clinical presentations consistent with and a diagnosis of ExDS. This suggests that one potential pathway for the development of ExDS is excessive dopamine stimulation in the striatum, but the significance of this in the larger context of ExDS unrelated to chronic cocaine abuse remains unknown.[33,34]

Even more supportive of central dopamine stimulation as a pathway is the fact that hypothalamic dopamine receptors are responsible for thermoregulation. These disturbances of dopamine neurotransmission may help explain the profound hyperthermia reported in many ExDS patients.[18] Post-mortem studies in these patients have demonstrated elevated levels of heat shock proteins (Hsp) – specifically Hsp 7. Hsps are found in nearly every cell and act to protect cell proteins from a variety of stressors. The central dopamine hypothesis also provides a link to psychiatric etiologies and the delirious presentation in patients with ExDS.

When available, cardiac rhythm analysis almost always demonstrates brady-asystole or pulseless electrical activity; ventricular dysrhythmias are rare, occurring in only a single patient in one study.[9] The majority of lethal ExDS patients who do die, do so shortly after a violent struggle, often within minutes after cessation of the struggle. This observation suggest that severe acidosis appears to play a prominent role in lethal ExDS-associated cardiovascular collapse and there may be some relation with the peaking of exogenous epinephrine levels in the first minutes after significant exertion.[35,36]

Obviously other components can impact the physiology of these individuals, including baseline hydration status, which can impact electrolyte balance and renal function, and need to be taken into consideration when evaluation these cases. Hyperthermia is often associated with subjects exhibiting signs of ExDS, but it not require to make the diagnosis. Hyperthermia is felt to be a finding supporting the individual's loss of auto-regulation and is caused by the ExDS. In the majority of the fatal cases of ExDS, hyperthermia is present and has been commented by Deborah Mash as being a harbinger of death.

## 8. Differential diagnosis

Members of the general public, law enforcement, emergency medical service workers, first responders, and even highly trained medical personnel cannot discern the cause of an acute behavioural disturbance by observation alone nor is it necessary that they do so. All that is required is that they be able to recognize that symptoms consistent with ExDS constitute a medical emergency, leading to the goal of rapid control and initiation of therapeutic interventions.

Several specific entities that cause altered mental status and may mimic ExDS and deserve specific mention. Diabetic hypoglycemic reactions, heat stroke, thyrotoxicosis, serotonin syndrome and neuroleptic malignant syndrome (NMS) all share some clinical characteristics with ExDS. Psychiatric issues may also mimic ExDS. Psychotropic drug withdrawal or non-compliance, substance abuse and many psychiatric conditions themselves, including acute paranoid schizophrenia, bipolar disorder, and even emotional rage from acute stressful social circumstances, may mimic an ExDS-like state.

## 9. Acute treatment

Without clear case definitions and prospective clinical studies, treatment of ExDS remains largely speculative and consensus-driven, directed towards supportive care and reversal of obvious clinical and laboratory abnormalities. In subjects who do not respond to verbal calming and de-escalation techniques, physical control measures are necessary before medical assessment and intervention can be initiated, and medical staff protected. This should be accomplished as rapidly and safely as possible. The use of multiple personnel with training in safe physical control measures is to be encouraged. It should be noted there are well-documented cases of ExDS deaths with minimal restraint such as handcuffs without ECD or maximal "hogtie" restraint use. There are no clinical or laboratory data that support that the use of prone or supine restraint will have any negative physiologic impact on these individuals.

Recent research indicates that physical struggle may be a greater contributor to catecholamine surge and metabolic acidosis than other causes of exertion or noxious stimuli.[37] There seems to be little doubt about the occurrence of acidosis in these situations, but whether or not epinephrine and norpnephrine are contributors is not clear and, at least partly dependent on the experimental model chosen – even in humans. This requires further research. Since these both cause acidosis and hypercatecholaminemia, both would be expected to contribute to poorer outcomes in ExDS, and therefore specific Use of Force physical control methods employed should be chosen to minimize the time spent struggling, while safely achieving safe and rapid physical control.

Once physical control is attained, medical assessment and treatment should be immediately initiated. Ideally, EMS should be present and prepared to resuscitate before definitive law enforcement officer control measures are initiated when possible. This requires coordination between law enforcement and EMS working in a collaborative effort with these patients.

Treatment options including sedative or dissociative agents such as benzodiazepines and ketamine, appear to be used regularly, but there is no solid evidence yet to prove that these actually improve outcome. In cases in which a core body temperature can be obtained and is elevated, appropriate cooling measures can be initiated.

The ExDS Workshop Panel, convened in April 2011 in Seattle by the NIJ's Technology Working Group (TWG) on Less-Lethal Devices, designed a useful two sided pocket card for use by law enforcement officers and EMS providers.(see Fig. 1). The card identifies the major presenting signs and symptoms to assist law enforcement personnel (and others) with recall and subsequent documentation, as well as a list of the treatment goals of ExDS which are: Identify, Control, Sedate, and Transport.

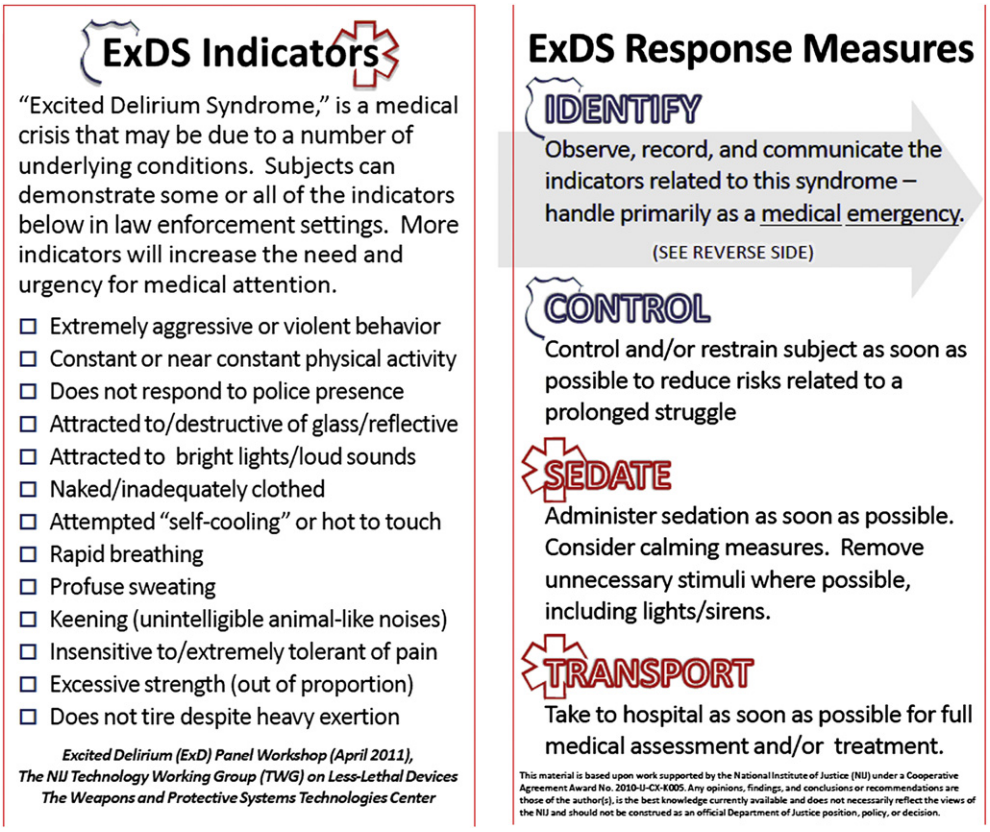


**Fig. 1.** Excited Delirium Syndrome pocket card (front and back) for law enforcement and EMS providers created by the work of the National Institute of Justice Technology Working Group (TWG) on Less-Lethal Devices (printed with permission from the NIJ).

## 10. Future directions

The basic issue surrounding the study of ExDS and proposed therapeutic interventions is the lack of well-defined, consistent epidemiological case definition. When a death occurs while in custody, there is often the additional challenge of separating any potential contributions made by restraint and control measures from those of the underlying pathology.

The official report from this multi-professional workshop is expected to be published in July 2011. It will recommend pathways for future research. This may include several areas and disciplines. Animal models should be developed to begin to better understand the pathophysiology of ExDS. In humans, a consistent case definition should be developed and applied in a large epidemiologic prospective study or from a national or international database of suspected cases, including those who survive. At a molecular level, and based upon post-mortem cocaine-associated ExDS brain tissue, there may be a genetic basis for susceptibility to ExDS.

Development of a national orphan case report registry is necessary to begin to define the evolution of ExDS, and might eventually provide for earlier recognition of individuals at risk. For these purposes, thorough documentation of the patient's signs and symptoms along with appropriate lab testing and documentation should occur in suspected ExDS cases. Creating this registry would also allow the scientific community to begin the process of identifying common characteristics as well as assessing the efficacy of various therapies.

We commend the NIJ for their efforts to examine this complex and controversial issue that has a significant impact on the law enforcement and medical community alike.

*Conflicts of interest*

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None declared.

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